Pulmonary Lymphoma of Large B-cell Type Mimicking Wegener’s Granulomatosis


Abstract
A 27-year-old man with a primary pulmonary lymphoma of large B-cell type is described. Symptoms involved both the upper and lower respiratory tract. A chest roentgenogram showed a dense mass with cavitation. Transbronchial biopsy specimens revealed no atypical cells, rather they demonstrated granulomatous infiltration and vasculitis consistent with but not conclusively diagnostic of Wegener’s granulomatosis. The pulmonary mass became smaller after sulfamethoxazole-trimethoprim therapy. These features suggested Wegener’s granulomatosis. However, an open biopsy specimen was diagnostic for diffuse lymphoma of large B-cell type. High-grade pulmonary lymphoma should be considered in the differential diagnosis of patients with clinical and pathologic features suggesting Wegener’s granulomatosis.

Key words: non-Hodgkin’s lymphoma, lung, large-cell type

Introduction
Pulmonary lymphoma is uncommon, representing less than 1% of primary lung cancers (1). This entity creates unusual diagnostic difficulties because of its rarity and manifestations that overlap those of infectious and other non neoplastic disorders. Careful clinical and radiologic evaluation must be followed by an optimal procedure for obtained diagnostic tissue. We report a case of large B-cell type non-Hodgkin’s lymphoma occurring in the lung with clinical features as well as microscopic findings in a transbronchial biopsy specimen that mimicked Wegener’s granulomatosis, creating a major diagnostic problem.
Fiberoptic bronchoscopy was performed, including bronchial washing and brushing as well as multiple transbronchial biopsies; in all, we carried out bronchoscopic examination on three occasions. These biopsy specimens showed histologic findings of “pulmonary angiitis and granulomatosis” as seen in Wegener’s granulomatosis or lymphomatoid granulomatosis (2, 3). The granulomatous change was associated with destruction of cartilage, and infiltrating neutrophils were seen to damage the intima of venules (Fig. 3A, B). Multinucleate giant cell or fibrinoid necrosis was not seen. No acid-fast bacilli, fungi, or malignant cells were detected by cytologic examination. Cultures of bronchial washings yielded no growth of bacteria or fungi. A renal biopsy specimen was normal.

Definitive diagnosis would have required surgical resection, but lobectomy of the right upper lobe was believed to be necessary due to the size of the mass. In view of the symptoms involving both the upper and lower respiratory tract, and findings in the biopsy specimens, a presumptive diagnosis of a limited form of Wegener’s granulomatosis was made, although other types of cavitary lung masses remained under consideration. The criteria of the American College of Rheumatology (4) were considered to favor Wegener’s granulomatosis, and sulfamethoxazole-trimethoprim therapy was initiated empirically in January 2000. Three weeks later, a chest roentgenogram and computed tomography demonstrated that the mass in the right upper lobe had regressed. C-reactive protein level and the erythrocyte sedimentation rate were also decreased from the values noted on admission to 1.7 mg/dl and 35 mm/h. However, in February, new nodular shadows were apparent in both lungs by computed tomography (Fig. 4). Gallium scintigraphy showed essentially similar lung uptake in the right upper lobe as on admission; no other uptake was detected. A nodule was resected from the posterior segment of the right upper lobe by video-assisted thoracic surgery (VATS) to obtain a diagnostic specimen.

Microscopic examination of this nodule showed diffuse proliferation of large, highly atypical cells intermingled with a much smaller number of inflammatory cells (Fig. 5). No variation in degree of atypism was observed among these tumor cells. Immunohistochemically, the tumor cells expressed leukocyte common antigen (CD45) and CD20, a B-cell marker (Fig. 6) on the cell surface; they were not stained for epithelial membrane antigen, cytokeratin, carcinoembryonic antigen, alpha-fetoprotein, human chorionic gonadotropin, or a T-cell marker (CD45RO). No vasculitis or granulomatous lesion was observed in the VATS specimen. Thus, a diagnosis of diffuse large B-cell non-Hodgkin’s malignant lymphoma was made. Moreover, the clinical stage was judged to be IV according to
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Figure 2. Gallium scintigram on admission shows an abnormal uptake extending from the right upper pulmonary lobe to the right hilum, as well as a slightly increased uptake in the area of the nose.

Figure 3. Histopathologic appearance of transbronchial biopsy specimens obtained from the mass in the anterior segment of the right upper lobe. A) Granulomatous lesion with lymphoid cells, plasma cells, and neutrophil infiltration (HE, ×100). B) Intimal destruction of a venule by infiltrating neutrophils (HE, ×200).

Figure 4. Computed tomogram taken obtained in February 2000 shows new nodules in the right upper lobe.

the Ann Arbor classification (5) because the disease was disseminated in both lungs. Soluble interleukin-2 receptor concentration in serum, a marker for lymphoma, was not increased (626 IU/ml) at the time of the VATS biopsy.

Treatment with combination chemotherapy consisting of cyclophosphamide, adriamycin, vincristine, and prednisolone (CHOP) was initiated with a repeat course given on days 21 to 28. Despite a total of two courses of CHOP, radiographically...
Lymphoma-Wegener's Granulomatosis Mimicry

Figure 5. Microscopic appearance of the video-assisted thoracic surgery (VATS) biopsy specimen, showing diffuse proliferation of medium-sized to large atypical cells with cleaved and noncleaved nuclei (HE, ×400).

Figure 6. The tumor cells show immunoreactivity for the B cell marker, CD20 (L26, ×400).

demonstrated pulmonary shadows did not decrease. Various additional combinations of chemotherapeutic agents did not change this lesion; however, the tumor did not show further dissemination. The patient has remained alive, with no worsening apparent at 9 months after the VATS biopsy.

Discussion

The most widely accepted criteria for designating a lymphoma in the lung as a primary lesion are those of Saltzstein (6). By these criteria, which were met in the present case, lymphoma affecting the lung must show no evidence of extrathoracic dissemination for at least 3 months after the initial diagnosis to be a primary neoplasm. Primary pulmonary lymphoma is rare; in a study of 1,269 cases of lymphoma, only 0.34% were believed to have a pulmonary origin (7). Most of these were low-grade, small B-cell lymphomas that originated from the mucosally associated lymphoid tissue of the bronchus (8, 9). High-grade (large cell) B-cell lymphomas together with predominantly angioimmunoproliferative lesions (lymphomatoid granulomatosis) account for most of the remaining tumors.

A histologic diagnosis of high-grade primary pulmonary lymphoma usually is easily made from surgical specimens, based on established pathologic features including a monomorphic cellular infiltrate, cytologic atypia, mitotic activity, and necrosis. Cordier et al (9) reported that even transbronchial biopsy specimens showed lymphomatous involvement in five of seven cases of high-grade lymphoma. In the present case, however, multiple transbronchial biopsy specimens obtained during three bronchoscopic procedures showed no atypical cells. Instead, the tissue showed inflammatory granulomas associated with vascular infiltration and cartilage destruction, consistent with Wegener's granulomatosis. Some reported cases of high-grade lymphoma have been accompanied by vascular infiltration or cartilage destruction, but lymphoma cells were consistently detected in the specimen (10). Further, laboratory data did not suggest neoplastic or infectious disease in the present case. Although definitive pathologic features and specific laboratory findings of such as elevation of C-ANCA were not present, a presumptive diagnosis of limited Wegener's granulomatosis could be made according to the criteria of the American College of Rheumatology (4). Malignant disease appeared very unlikely. Since limited Wegener's granulomatosis often responds to sulfamethoxazole-trimethoprim therapy alone, and definitive diagnosis would have required a lobectomy, we observed the patient during a therapeutic trial of sulfamethoxazole-trimethoprim. Transient regression of the lesion proved to be misleading, delaying a definitive diagnosis of malignant lymphoma for about a month. In retrospect, the differential diagnosis of cavitory lesion must include the possibility of high-grade lymphoma, and surgical biopsy must be performed without delay if a definitive diagnosis cannot be established by less invasive procedures. Further, diagnosis of Wegener's granulomatosis from transbronchial biopsy specimens is very difficult, so full evaluation of this possibility also required a large surgically obtained biopsy specimen (11). Thus, a surgical procedure was needed to establish a definitive diagnosis promptly, even though lobectomy was required.

In the present case, the upper respiratory symptoms together with the pathologic features strongly suggested Wegener's granulomatosis. We are aware of no other report of a high-grade pulmonary lymphoma associated with upper respiratory symptoms. Direct invasion of lymphoma cells into the upper respiratory tract was not demonstrated in our case. The mechanism causing upper respiratory symptoms in the present case is uncertain, but we suspect that these symptoms may be related to the pulmonary lymphoma. Some lymphoproliferative disorders may well result from more than one type of immune response, possibly involving activation of both T- and B-lymphocytes (12, 13) to a variable extent. Furthermore, reactive cells and infiltrating neutrophils, in addition to lymphoma cells...
themselves, may express cytokines such as interleukin-8 (14). On the other hand, nasal mucosal inflammation may result in production of several cytokines such as interleukin-6, interleukin-8, and tumor necrosis factor-α (15) that could affect the nasal and oral mucous membranes.

In the present case, the pulmonary mass became smaller after sulfamethoxazole-trimethoprim therapy, as has been seen in cases of limited Wegener’s granulomatosis (16, 17). This response would be unusual because large B-cell lymphomas usually progress rapidly. Perhaps sulfamethoxazole-trimethoprim therapy suppressed infiltration of reactive cells and neutrophils in reaction to the tumor by interfering with formation of specific oxygen-derived radicals (18). Spontaneous regression of non-Hodgkin’s lymphoma also rarely may occur (19). The additional possibility remains that sulfamethoxazole-trimethoprim had an effect against a superimposed infection that was not detected by bronchoscopy or sputum examination. For whatever reason improvement occurred, and the response masked the diagnosis of aggressive lymphoma.

Because the radiologic and pathologic features of lymphomatoid granulomatosis and Wegener’s granulomatosis diseases can be similar, their important difference was discussed (20). Both diseases appear as pulmonary angitis and granulomatosis (2, 3). Typical lymphomatoid granulomatosis, however, is characterized by heterogeneous infiltrates including atypical cells (21). In our case no atypical cells were detected, so we made a presumptive diagnosis of Wegener’s granulomatosis rather than lymphomatoid granulomatosis. Lymphomatoid granulomatosis can transform to high-grade lymphoma, and the B-cell lymphoma of the present case might have arisen in this manner (21–23). Our case suggests that not only lymphomatoid granulomatosis but also high-grade B-cell pulmonary lymphoma can be clinically similar to Wegener’s granulomatosis. These diseases behave aggressively, and definitive diagnosis must be established as soon as possible. Awareness of the variable histologic and symptomatic features of high-grade primary pulmonary lymphoma is very important as well as careful morphologic and immunologic examinations.

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References